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**RESPIRATORY CHEMOSENSITIVITY AND
RESISTIVE LOAD SENSATION INFLUENCES ON
VENTILATORY CONTROL DURING EXERCISE**

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**U S ARMY RESEARCH INSTITUTE
OF
ENVIRONMENTAL MEDICINE
Natick, Massachusetts**

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**RESPIRATORY CHEMOSENSITIVITY AND
RESISTIVE LOAD SENSATION INFLUENCES
ON VENTILATORY CONTROL DURING EXERCISE**

by

Stephen R. Muza, Leslie Levine and William A. Latzka

May 1990

U.S. Army Research Institute of Environmental Medicine
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EXECUTIVE SUMMARY

This study examined the affect of added inspiratory resistance (R_i) on breathing patterns and work performance during progressive intensity exercise, steady-state exercise and constant effort work. Its aim was to determine the relationship between respiratory sensations and hypercapnic responsiveness to exercise breathing patterns and external work performance. We found that mild R_i (5 cm $H_2O \cdot L^{-1} \cdot sec^{-1}$) did not alter peak oxygen uptake, peak power output, or steady-state submaximal work duration. However, during progressive intensity exercise, changes in the pattern of breathing, particularly a reduction of mean inspiratory flow (an index of respiratory drive) occurred with the imposition of the R_i , whereas, the breathing cycle timing components were relatively unchanged. During submaximal steady-state exercise, added R_i decreased mean inspiratory flow but prolonged the duty cycle thus maintaining minute ventilation. Despite its effects on breathing pattern and respiratory work, imposition of added R_i did not affect constant effort functions to cycle ergometry, suggesting that perception of respiratory effort did not significantly influence the perceived effort of the exercise task. Exercise minute ventilation was found to be strongly correlated to subjects' ventilatory hypercapnic responsiveness. We demonstrated that of the components of minute ventilation, timing and respiratory drive, the latter was correlated to hypercapnic responsiveness but the former was not during both maximal intensity and submaximal exercise tasks. The subjects' perception of added inspiratory resistance (magnitude estimate) did affect their pattern of breathing when added inspiratory loads were present, but the ventilatory responsiveness to hypercapnia was the stronger determinant of exercise hyperpnea. The finding that both submaximal and maximal exercise minute ventilation was strongly correlated to subjects' ventilatory hypercapnic responsiveness, suggests it may be possible to screen soldiers who are more prone to work performance decrements when wearing a CB mask. Moreover, the observation that respiratory drive (rate of respiratory muscle force development) was correlated both to oxygen uptake and hypercapnic responsiveness during both maximal intensity and submaximal exercise tasks, suggests that respiratory muscle strength training programs may help alleviate the adverse respiratory sensations experienced by soldiers wearing CB masks. Further research into screening programs and if respiratory muscle training improves the pattern of exercise hyperpnea with concomitant amelioration of adverse respiratory sensations will need to be conducted.

INTRODUCTION

The U.S. Army must be prepared to engage in military operations in a nuclear, biological and chemical (NBC) contaminated environment. During these operations soldiers wearing MOPP (Mission Oriented Protective Posture) gear will engage in a variety of tasks that require physical exercise. Soldiers are provided with individual protective equipment (MOPP gear) to protect against NBC contamination. One element of the MOPP gear is the chemical-biological (CB) protective mask. The new M40, and older M17 field and M25 tank series of CB masks can provide respiratory protection against field concentrations of all known chemical and biological agents in vapor and aerosol form. Filter elements located in the inspiratory circuit of the CB masks filter contaminated air to remove the agents. Wearing the CB masks impairs the performance of moderate and high activity tasks encountered in military operations (23,24,28,35). The mask's principal limitation on the tolerance to physical activity is the resistance to inspiratory and expiratory airflow developed by the mask's filter elements and valve assemblies.

Numerous studies (6,12,13,20,22,28,40,41) have provided data for determining tolerable limits of external breathing resistance. However, a common observation of many of these studies is the considerable variability between subjects in the degree of discomfort felt and tolerance to exercise under similar conditions of physical stress while breathing through a mask (6,12,17,22,35,41). It is well known that the ability of healthy subjects to judge magnitudes of added loads to breathing varies widely (26,30). But, little is known concerning how an individual's sensitivity in perceiving added loads to breathing influences their regulation of ventilation when breathing is opposed and consequently their ability to perform hard work. Therefore, this study examined the relationship between an individual's ability to judge the size of added inspiratory resistive loads and the means by which they attempted to maintain ventilation when breathing through an added inspiratory resistance similar to a CB mask. Our hypothesis is that there is a direct positive relationship between individual perceptual performance in scaling added resistive loads and the degree of ventilatory load compensation exhibited when breathing is opposed by wearing a CB mask. Specifically, the study had the following aims:

1. Demonstrate a wide range of perceptual performance in scaling added inspiratory resistance in normal soldiers.
2. Demonstrate a wide range of respiratory sensitivity to hypercapnia in normal

soldiers.

3. Determine the effect added inspiratory resistance has on breathing patterns and work performance during: progressive intensity exercise; steady-state exercise; and constant effort exercise.
4. Determine the relationship between respiratory sensations and hypercapnic responsiveness to exercise breathing patterns and work performance.
5. Evaluate the effects of added resistance to breathing on the subjective regulation of exercise intensity by perceived exertion.

BACKGROUND

Although the first use of CB masks during military operations dates back to World War I, the development of standards for acceptable levels of breathing resistance of protective masks did not occur until World War II. Several studies by Silverman et al. (39,40) investigated the effects of breathing against added resistance while working at various rates on a bicycle ergometer. Healthy male subjects exercised for 15 minute periods at work rates ranging from 0 to 1660 kgm·min⁻¹ with added inspiratory resistances ranging from 0.6 to 10.6 cm H₂O measured at a flow rate of 85 L·min⁻¹. Increases in the resistance to breathing resulted in decreased submaximal oxygen uptake and minute ventilation at work rates above 830 kgm·min⁻¹. Most subjects were able to tolerate the added resistance provided the total external respiratory work did not exceed 2.5 kgm·min⁻¹ at the low workloads and 13.3 kgm·min⁻¹ at the high workloads. These data have provided the basis for all modern-day military CB mask design criteria and certification tests. Numerous studies have extended these original observations with the goals of determining a) acceptable levels of resistance for industrial and military respiratory apparatus; b) the degree of work impairment that occurs when wearing protective respiratory equipment; and c) the physiological responses which limit the tolerance to physical activity when breathing is opposed.

In 1960, Cooper (13) suggested standards of resistance which he expressed as the rate of respiratory work done on a breathing apparatus per minute ventilation. The maximum respiratory work rate done on a mask expressed in kgm·min⁻¹ was arbitrarily set at one-fourth of the minute ventilation (L·min⁻¹). Since Silverman et al. (40) had suggested lower levels of respiratory work, Cooper acknowledged that this standard may represent an excessive resistance and that the ideal mask may have

a resistance one-half of this standard. Thirteen years later, Bentley et al. (6) re-evaluated tolerance to added resistance to breathing in 158 mine rescue workers during exercise. The added inspiratory resistance ranged from 1.9 to 19.5 cm $\text{H}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}^{-1}$ measured at 85 $\text{L}\cdot\text{min}^{-1}$. After completion of the exercise, each subject selected one of four statements which most closely described his sensation of the effect of the resistance on his breathing. The results indicated that peak inspiratory pressure and the inspiratory work rate per liter of inspired air were closely correlated with the sensation of dyspnea. From their data, Bentley et al. formulated a standard for acceptable resistance such that 90% of the population tested would not experience dyspnea. They determined the level of external respiratory work done on a mask should not exceed 0.17 $\text{kgm}\cdot\text{L}^{-1}$ of inspired air, or under steady flow conditions the pressure drop across the inspiratory valve and filter should not exceed 17.0 cm H_2O . This level of tolerable external respiratory work is below that suggested by Cooper (13), but above that derived by Silverman et al. (40).

Given the pressure-flow characteristics of the M25, M40 and M17 series of CB masks, and applying Bentley et al.'s results, we predict that discomfort in breathing would be experienced by 10% of the wearers at minute ventilations of 55, 67 and 89 $\text{L}\cdot\text{min}^{-1}$ for each mask, respectively. These levels of minute ventilation are commonly attained during moderate intensity exercise and may represent the threshold above which the widespread development of dyspnea may impair soldier work performance.

Many studies have investigated the performance decrement that can be attributed to CB mask wear. Some of the performance decrements measured are not due to respiratory stress but to other nonresistive characteristics of the mask facepiece (skin irritation, restricted visual field, psychological problems) (32). Generally, little effect of resistance is seen on performance during low intensity, long-term activities. However, with tasks that demand a high percentage of an individual's maximal aerobic power, performance seems to be dependent on breathing resistance (24). Cummings et al. (15) reported that wearing a CB mask increased the time to accomplish a one-half mile run by 11%. Lotens (28) found a 16% performance decrement during 400 m and 3 km runs while wearing the C-3 respirator. Similar results were obtained during British studies of their S-6 respirator. Most studies have tested work performance of men wearing masks using both fixed task-variable rate and fixed rate-variable time end points. A different approach to evaluating work

performance is the use of the Borg psychophysical scale of perceived exertion to set and adjust exercise intensity. Smutok *et al.* (42) demonstrated that subjects are able to subjectively regulate their exercise intensity. However, no data have been reported in which subjects set and regulate their exercise intensity by perceptual feelings with and without an added inspiratory resistance. Such a study could provide a novel means of evaluating the performance decrement related to mask wear and deriving a model capable of predicting soldier work performance while wearing a CB mask.

The mechanism by which added resistance to breathing impairs work performance is potentially complex. Cerretelli *et al.* (12) investigated the effects of three levels of added resistance (2.5, 9.0, 17.5 cm H₂O L⁻¹ s⁻¹) applied to inspiration and expiration during treadmill exercise at various intensities. Increasing added resistance to breathing decreased minute ventilation and endurance time at each level of exercise. The reduction in ventilation was directly proportional to the increase in resistance. Maximal oxygen uptake ($\dot{V}O_2$ max) was reduced, but the relationship between oxygen uptake and submaximal workload was not altered. When breathing through added resistance, the relative hypoventilation resulted in an increase of alveolar carbon dioxide, which may impair the capacity for work. Cerretelli *et al.* (12) also observed that at the highest levels of exercise the work could no longer be tolerated when the intrathoracic pressure difference between inspiration and expiration exceeded 100 cm H₂O. In an additional experiment done at rest, resistance was added until the subject could not continue. Again, the maximum intrathoracic pressure difference was 100 cm H₂O. They speculated that when intrathoracic pressure swings approach this level, some protective mechanism intervenes to limit the respiratory work.

In 1972, Hermansen *et al.* (20) investigated the respiratory and circulatory response to added air flow resistance during exercise. Using an M9 gas mask (inspiratory resistance 9 cm H₂O L⁻¹ s⁻¹, expiratory resistance 2.6 cm H₂O L⁻¹ s⁻¹) they observed reductions of minute ventilation and maximal oxygen uptake consistent with the report of Cerretelli *et al.* (12). Likewise, at all submaximal workloads up to approximately 75 percent of $\dot{V}O_2$ max the oxygen uptake-workload relationship was unaffected by mask wear. Hermansen *et al.* noted that ventilatory rates were lower with the mask on and rose only to 30 breaths min⁻¹ during exercise. Additionally, average heart rates during submaximal exercise were higher when wearing the

mask but were similar at maximal exercise to those obtained without added resistance to breathing. The authors concluded that the level of added resistance imposed in their study compromised aerobic performance only at exercise intensities above 75% $\dot{V}O_2$ max.

Demedts and Anthonisen (17) obtained results similar to those previously reported (12,20) during exercise with three levels of increased inspiratory and expiratory resistance (2.5, 5.25 and 16.0 cm $H_2O \cdot L^{-1} \cdot s^{-1}$). Two additional observations were made. First, at each level of added resistance, maximum exercise ventilation was about 70 percent of the 15 second maximum voluntary ventilation measured with that resistance. However, the two lowest resistances did not diminish exercise tolerance, although they were readily detectable. Secondly, in four of the subjects examined, an important relationship was observed between an individual's ventilatory response to CO_2 and the degree of their respiratory effort while breathing against added loads. When breathing was opposed by added resistance, subjects with low CO_2 response curves minimized their ventilatory effort and let their alveolar CO_2 rise. Those subjects who were most sensitive to CO_2 increased their respiratory work in order to maintain alveolar CO_2 near normal. Consequently, the latter subjects' exercise intensity and duration were more limited by the added resistance. The authors concluded that the exercise limitation imposed by added resistance to breathing is dependent on the ventilatory limitations produced by the resistance and on the CO_2 responsiveness of the individual.

Concerning the latter mechanism, several studies have demonstrated that low responders to hypoxia or hypercapnia breathe less than high responders during exercise (29). Recently, D'Urzo *et al.* (18) reported that the ventilatory response below the ventilatory threshold was correlated with the subjects' CO_2 sensitivity. Furthermore, they showed that a mild increase of inspiratory resistance during progressive exercise to exhaustion altered ventilatory control at work loads that exceeded the ventilatory threshold. Subjects with higher CO_2 sensitivities produced greater inspiratory flows thus minimizing the load induced hypoventilation at maximum exercise. However, D'Urzo *et al.* did not report which of the volume and timing components of the exercise breathing pattern were correlated to subjects' CO_2 sensitivity. Nor has any study fully investigated the potential relationship between individual CO_2 responsiveness and limitation to steady-state exercise when wearing CB masks.

The studies of Cerretelli *et al.* (12), Hermansen *et al.* (20), Demedts and Anthonisen (17) and D'Urzo *et al.* (18) all demonstrate a reduction of minute ventilation during exercise with added resistance to breathing. Several investigators (14,23) have shown that this limitation of ventilation during exercise is the effect of attempts to minimize the total respiratory work by reducing the expiratory duration (T_e) of each breath in order to prolong the inspiratory duration (T_i). Craig *et al.* (14) studied 13 subjects who exercised to exhaustion on a treadmill while breathing through added inspiratory resistances (1.5 to 15.5 cm H₂O L⁻¹ s⁻¹) and expiratory resistances (2.0 to 3.9 cm H₂O L⁻¹ s⁻¹). Increasing the resistance to breathing, decreased the time to exhaustion. As ventilation increased in response to the exercise, T_e decreased while the T_i remained almost constant. A subsequent study by Johnson and Berlin (23) demonstrated in 10 subjects that a minimum T_e of 0.66 s corresponded to the voluntary termination of exercise. Accordingly, when wearing a CB mask, minute ventilation can increase in response to the metabolic demands of the exercise until the minimum T_e is reached. Thereafter, minute ventilation falls below the metabolic needs of the individual and impairs continued exercise performance.

A potential consequence of prolonged work while wearing a CB mask is respiratory muscle fatigue. During exercise with no opposition to breathing, ventilatory muscle endurance does not appear to constitute a limitation to exercise performance (3,10,21,45). Therefore, studies of respiratory muscle fatigue generally employ a mechanical load on breathing to produce the desired degree of fatigue (4,5,34). Respiratory muscle fatigue is usually measured as the inability to develop and maintain a target pressure or flow, decreased endurance time, or a shift toward lower frequencies of the muscles' electromyogram power spectrum (37). The work of breathing increases as the resistance to breathing is increased. The greater the fraction of the maximum pressure developed by the inspiratory muscles in order to breath across a resistance, the greater the energy demands of the muscle. Roussos and Macklem (37) found that the endurance time of the human diaphragm is less than 60 minutes when the transdiaphragmatic pressure (P_{di}) developed with each inspiration is greater than 40% of the subject's maximal P_{di} . Bellemare and Grassino (4,5) demonstrated that development of diaphragm fatigue was dependent upon both the relative P_{di} developed and the duration of the contraction or duty cycle ($T_i T_{tot}^{-1}$). This tension time index ($P_{di} P_{di,max}^{-1} T_i T_{tot}^{-1}$) was found to have a

critical value of about 0.15. Above this value, diaphragm fatigue would develop limiting ventilatory endurance time to less than 45 minutes. Most investigations of respiratory muscle fatigue have utilized large resistive loads and an experimentally imposed pattern of breathing of short duration to produce fatigue. The development of respiratory muscle fatigue has not been examined in working soldiers while wearing CB masks. Although it has been speculated that respiratory muscle fatigue is a limiting factor of work performance when wearing CB masks, this relationship has not been demonstrated.

In conscious humans the ventilatory response to mechanical loading is also modulated by neural responses mediated through conscious perception of the added load (2,16). Psychophysics is the scientific study of the relationship between stimulus and sensation. The psychophysical technique of magnitude estimation has been used to study respiratory sensations. This scaling technique assesses subjects' perceptual performance in judging the magnitude of a suprathreshold stimulus (eg. added resistance, elastance, volume).

Since 1978 numerous studies have concluded that the relationship between the perceived magnitude of added resistive loads and the intensity of the loads follows Stevens' psychophysical power law (7,8,9,19,26,27,30,31,43,50) where the perceived magnitude (Ψ) of a stimulus is related to the physical magnitude of the stimulus (ϕ), by a constant (K), and an exponent (η): $\Psi = K\phi^\eta$ (31). The exponent provides an index of the perceptual magnitude with which sensation is perceived as a function of stimulus magnitude.

Results of several studies (1,11,25,27) suggest that signals related to: 1) respiratory muscle force generation, and/or 2) motor command to the respiratory muscles, may contribute to the perception of added loads to breathing. Perceptual performance during a scaling task is very reproducible within a given subject but has been observed to vary greatly between subjects. For 10 duplicate studies in 10 subjects, Killian *et al.* (26) reported the intrasubject variation was very narrow (mean coefficient of variation, 7 percent), whereas intersubject variation was quite wide (mean coefficient of variation, 230 percent). Muza *et al.* (30) reported in ten healthy male adults, that the magnitude estimate ranged from 0.37 to 1.20. Little is known concerning the important question of whether or not an individual's perceptual sensitivity influences how they regulate ventilation when breathing is opposed.

Gottfried et al. (19) examined the relationship between perceptual performance and the ventilatory responses during resistive loading in normal subjects and chronically obstructed pulmonary diseased (COPD) patients. The normal subjects had lower thresholds for load detection and higher exponents for magnitude estimation than the COPD patients. The former exhibited a greater increase in occlusion pressure with inspiratory loading than the latter. These results suggest that high perceptual sensitivity to added respiratory loads is associated with improved ventilatory load compensation.

Muza et al. (30) examined the relationship between perceptual performance and load compensation responses to inspiratory resistance ($8 \text{ cm H}_2\text{O} \cdot \text{s}^{-1}$) added for one to three breaths in ten healthy subjects. Significant ($p < .05$) correlations were obtained between subject's perceptual performance and the first loaded breath mean rate of rise of inspiratory mouth pressure, minute ventilation and duty cycle. These results suggest that healthy subjects who have a greater perceptual performance in scaling added inspiratory loads are better able to preserve their ventilation when unexpectedly confronted with an added load.

The wide range of perceptual performance observed in the healthy adult population may account for the reported variability between subjects in the degree of discomfort felt and the tolerance to exercise under similar conditions of physical stress while breathing through a CB mask. Therefore, this study tested the hypothesis that there is a direct positive relationship between individual perceptual performance in scaling added resistive loads and the degree of ventilatory load compensation exhibited when breathing is opposed by wearing a CB mask.

METHODS

SUBJECTS

The physiological responses to added airflow resistance were examined in twelve male subjects. They received a medical examination and were informed of the purpose and procedures of the study, any known risks and their right to terminate participation at will without penalty. Each expressed understanding by signing a statement of informed consent. The physical characteristics of the subjects are presented in Table 1. The subjects' medical examination revealed no history of pulmonary disease or neuromuscular disorders and were of average or better physical fitness as measured by peak aerobic power tests.

The experimental protocol was conducted over four test days. Each subject was tested individually. All exercise was performed on a semi-supine, electrically braked, cycle ergometer. On the first day, each subject received instruction and practice on the equipment and testing procedures. Following this practice session each subject was then administered the first of two peak aerobic power tests ($\dot{V}O_2$ peak) and two self-paced work tests.

PEAK AEROBIC POWER TESTS

The peak $\dot{V}O_2$ tests were conducted under two different experimental conditions using a progressive intensity, continuous effort cycle ergometer protocol to exhaustion. The subject performed the test while breathing through a facemask that provided minimal opposition to breathing (control condition, R_0) and a mask configured to provide an inspiratory resistance of 5 cm $H_2O \cdot L^{-1} \cdot s^{-1}$ (experimental condition, R_5) (Figure 1). The two peak $\dot{V}O_2$ tests were conducted on separate test days. The subject sat on a cycle ergometer and breathed through a facemask (Rudolph #7900). The inspiratory ports of the mask were connected to one of two breathing circuits allowing selection of two resistive loads (R_0 and R_5). Inspiratory flow, measured with a pneumotachograph, was integrated to give inspiratory volume (V_I). Mouth pressure (P_m) was measured from a pressure port on the mask's face piece with a Validyne pressure transducer. Inspiratory and expiratory durations (T_i and T_e respectively) were determined from the mouth pressure tracing. End tidal P_{CO_2} was sampled and analyzed by an infrared CO_2 analyzer (Beckman LB-2). The

expiratory port of the mask was connected to the Sormedics Horizon MMC System for determination of respiratory exchange measurements ($\dot{V}O_2$, $\dot{V}CO_2$, RER and \dot{V}_E). Heart rate (HR) was obtained from an electrocardiogram and recorded periodically. Blood pressure was measured by auscultation. Before the exercise began and immediately after the peak $\dot{V}O_2$ test ended, an Environmental Symptoms Questionnaire was administered.

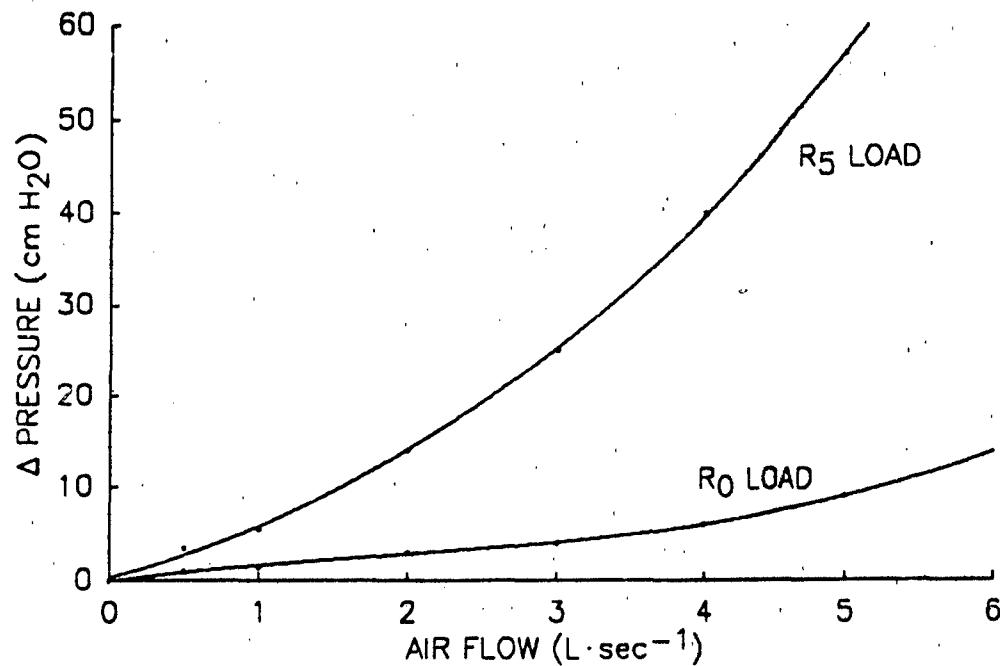


Fig. 1: Plot of pressure flow characteristics of the inspiratory breathing circuit.

TABLE 1
SUBJECT CHARACTERISTICS

S #	HEIGHT (cm)	WEIGHT (kg)	AGE (yr)	FVC* (%)	FEV ₁ * (%)	PEAK \dot{V}_{O_2} (ml·kg ⁻¹ ·min ⁻¹)
1	178	80	24	91	99	40
2	173	73	22	100	105	51
3	166	74	29	92	96	43
4	185	72	28	77	77	57
5	166	62	21	81	78	43
6	172	70	24	112	109	43
7	171	62	21	82	79	43
8	178	76	22	104	100	49
9	175	83	34	89	95	48
10	174	67	21	78	91	35
11	159	66	19	106	109	53
12	176	72	23	104	111	50
MEAN	173	72	24	93	96	46
S.D.	6	6	4	12	12	6

* Percent of age predicted normal

SELF-PACED WORK PROTOCOL

The purpose of this investigation was to determine the performance decrement produced by a CB mask and whether a relationship exists between work performance and sensitivity to respiratory stimuli. The subject was instrumented as described for the peak $\dot{V}O_2$ exercise tests. Two 30 minute self-paced work trials on the cycle ergometer were run with an appropriate rest period between each trial. Either the R_0 or R_1 breathing circuit was used. Presentation of the minimal or increased resistance first was balanced between subjects.

The subject was instructed how to adjust the cycle ergometer work load and practiced pedaling at the selected revolutions per minute. The two constant-effort trials were conducted with an initial power output of approximately 70% peak $\dot{V}O_2$. For the first minute of the constant-effort trial the subject maintained the initial power output. Then the subject controlled the load selector and made changes whenever necessary to maintain the prevailing level of effort constant over the next twenty-nine minutes. The subject's power output was continuously measured along with the previously described ventilatory and cardiovascular parameters. The performance decrement incurred by the inspiratory resistance was quantified as a function of the power output each subject was able to sustain with and without the added inspiratory resistance. The measured performance decrement was compared to each subject's sensitivity to respiratory stimuli to evaluate the influence of respiratory sensations on power output performed.

The second test day consisted of two test phases: sensitivity to respiratory stimuli and steady-state exercise.

SENSITIVITY TO RESPIRATORY STIMULI

Two tests were administered to evaluate each subject's sensitivity to mechanical and chemical respiratory stimuli: a) inspiratory resistance load magnitude estimation and b) ventilatory responsiveness to carbon dioxide rebreathing. First, the subject's forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_{1.0}$) were measured using a Collins 9 L respirometer.

For the resistive load magnitude estimation test, a resistance manifold, similar to

one described by Wiley and Zechman (44), consisting of eleven sintered bronze discs arranged in series in a 2.75 inch diameter lucite tube was used. Rubber stoppers were placed in ports between the discs to produce the desired load. Subjects were seated behind a screen and breathed room air through a Collins two-way "J" valve whose inspiratory port was attached via 1.5 inch diameter plastic tubing to the resistance manifold. Mouth pressure (P_m) was sampled from the middle chamber of the two-way "J" valve by a differential pressure transducer (Validyne Model MP45-1-871, range ± 50 cm H₂O). Inspired volume measurements were obtained by electronically integrating flow (\dot{V}) which was measured by a pneumotachograph interposed between the two-way "J" valve and mouthpiece and connected to a differential pressure transducer (Validyne Model MP45-1-871, range ± 2 cm H₂O). All measurements were simultaneously recorded on a direct writing polygraph (Western Graphtec) and an analog tape recorder (Hewlett Packard, model 3968A).

LOAD SCALING PROTOCOL

Five suprathreshold resistive loads (5.8, 8.0, 12.5, 20.0 and 31.0 cm H₂O L⁻¹ s⁻¹) were used in this part of the study. The subjects were instructed that after their breathing pattern had stabilized, suprathreshold resistive loads would be added to inspiration. The load intensity was randomized and each loaded breath was separated by several unloaded breaths. A light cue was presented on the preceding expiration for each inspiratory load. The subjects' task was to squeeze a handgrip dynamometer coincident with the loaded breath to express the pattern and the perceived magnitude of each added resistive load (cross-modality matching). At the onset of the experimental run, the subjects were presented a moderate size load (12.5 cm H₂O) and instructed to develop a moderate handgrip force. No further information was provided to the subjects regarding the load range nor was any statement made when the moderate size load randomly appeared during the experimental run. Each of the five resistive loads was presented four times each during inspiration for a single breath. The subjects monitored an oscilloscope display of their airflow and were instructed to track their airflow at 0.5 L.sec⁻¹ for the duration of the loaded inspiration.

Stevens' power law ($\Psi = K\phi^n$) was used to define the relationship between the

subjects' estimate of the added loads (magnitude estimate or ME) and the physical stimulus. The exponent (η) was obtained by performing a logarithmic transformation: $\text{Log } \Psi = \eta \text{ Log } \phi + \text{Log } K$ (eq. 1) where η becomes the slope of the line when $\text{Log } \Psi$ is plotted against $\text{Log } \phi$. The slope, η , is defined as the subject's ME. For each subject, the means of the estimate (mm deflection of grip), and corresponding peak P_m were determined for each load level. Then each subject's solution to equation 1 was found for inspiratory resistive loads with peak P_m taken as the physical stimulus and handgrip deflection taken as the perceived magnitude. The slopes, intercepts and correlation coefficients of the log transformed stimulus-response relationships were calculated by the method of least squares.

HYPERCAPNIC RESPONSIVENESS PROTOCOL

Subjects' ventilatory response to CO_2 (hypercapnic responsiveness) was measured by the rebreathing technique (36). For this rebreathing method, the subject rebreathes from a small bag containing an initial mixture of CO_2 (7%) and C_2 (balanced) at a volume one liter greater than his vital capacity for a period of four minutes during which the subject's alveolar CO_2 ($P_A\text{CO}_2$) increases. Minute ventilation and $P_A\text{CO}_2$ were measured every thirty seconds during the procedure. Hypercapnic responsiveness, $(\Delta\dot{V}_E/\Delta P_A\text{CO}_2)$, was calculated using least squares regression.

STEADY-STATE EXERCISE PROTOCOL

This phase of the investigation was designed to evaluate the relationship between an individual's sensitivity to respiratory stimuli and the degree of ventilatory load compensation exhibited when breathing is opposed by added resistance during exercise. The subject sat on a cycle ergometer and breathed through a facemask (Rudolph #7900). The inspiratory ports of the mask were connected to one of two breathing circuits allowing selection of two resistive loads (R_0 and R_1). The subject was instrumented as described for the peak VO_2 exercise tests.

A stable breathing pattern was then recorded with either the R_0 or R_1 inspiratory resistance (control period) before starting the steady-state exercise. The exercise period was 30 minutes long. During the first 5 minutes the power output was adjusted in order to obtain a measured oxygen uptake equal to 60% of the subject's

measured peak $\dot{V}O_2$. Before the exercise began and immediately after the constant effort exercise test ended, an Environmental Symptoms Questionnaire was administered.

On the third day the second self-paced work and peak $\dot{V}O_2$ tests were administered. The second steady-state exercise test was performed on the fourth test day.

STATISTICAL ANALYSIS

A repeated measures ANOVA was utilized to determine if added resistance to breathing altered the ventilatory responses during each of the exercise protocols. Linear regression analysis (least squares) was used to test for relationships between subject's sensitivity to CO_2 and added resistance and the exercise pattern of breathing. A stepwise multiple regression analysis was used to test for relationships between selected breathing parameters.

RESULTS AND DISCUSSION

VENTILATORY SENSITIVITY TO HYPERCAPNIA AND ADDED INSPIRATORY RESISTANCE

The ventilatory responsiveness to CO_2 for each subject is presented in Table 2. The group mean response ($2.67 \text{ L} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1} \text{ P}_\text{A}\text{CO}_2$) was very close to the value ($2.53 \text{ L} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1} \text{ P}_\text{A}\text{CO}_2$) reported in previous studies (38) involving larger subject populations. Hypercapnic sensitivity ranged from 0.57 - $4.75 \text{ L} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1} \text{ P}_\text{A}\text{CO}_2$ with a coefficient of variation of 45%. Therefore, our subject population's ventilatory responsiveness to hypercapnia demonstrated the expected distribution and range for a normal, healthy, adult population.

Each subject's perceptual sensitivity (ME) to added inspiratory resistive loads is also presented in Table 2. The group mean (0.58) is similar to exponents obtained with identical experimental conditions by previous investigators (0.73, ref 31,46). Perceptual sensitivity ranged from 0.27 to 1.10, with a coefficient of variation of 47%. Again, this range and distribution was consistent with previous studies of normal young adults (31,46).

Regression analysis indicated that there was a significant ($p < 0.05$) correlation ($r = 0.66$) between these two measures of sensitivity to respiratory stimuli. Thus, these two measures of sensitivity to respiratory stimuli shared 33% of the variance. This finding suggests that sensitivity to respiratory stimuli, whether chemical or mechanical, may not only be specific to a given stimulus modality, but may also be partially influenced by a central nervous system's overall sensitivity to afferent input.

TABLE 2
SUBJECT'S HYPERCAPNIC RESPONSIVENESS AND
MAGNITUDE ESTIMATION OF ADDED LOADS

S #	$\Delta\dot{V}_E \Delta P_A \text{CO}_2^{-1}$ (L·min ⁻¹ ·mmHg ⁻¹)	MAGNITUDE ESTIMATE
1	1.49	0.69
2	4.75	0.54
3	3.56	0.69
4	3.85	1.10
5	0.57	0.16
6	2.52	0.47
7	1.75	0.41
8	2.70	0.50
9	3.75	1.09
10	1.26	0.27
11	3.36	0.53
12	2.46	0.52
MEAN	2.67	0.58
S.D. (±)	1.19	0.27

VENTILATORY AND METABOLIC RESPONSES TO PROGRESSIVE INTENSITY EXERCISE

All subjects completed two progressive intensity exercise bouts to fatigue on a semi-supine cycle ergometer. Inspiratory resistance was either R_0 or R_s . Neither the peak external work achieved (261 ± 26 and 257 ± 30 W with R_0 and R_s , respectively) nor the peak $\dot{V}O_2$ (46.2 ± 6.0 and 44.7 ± 5.8 ml kg⁻¹ min⁻¹, R_0 and R_s , respectively) were significantly altered by addition of the added inspiratory resistance. Therefore, this level of inspiratory resistance did not limit the subjects' ability to briefly achieve their maximal external work or peak aerobic energy expenditure.

As work intensity increased, minute ventilation increased proportionally to metabolic demand (Fig. 2). As expected, minute ventilation was highly correlated ($p < 0.01$) to oxygen uptake. With the R_0 and R_s loads, minute ventilation increased 3.4 and 2.92 L min⁻¹ for each ml kg⁻¹ min⁻¹ increase of oxygen uptake respectively. However, the exercise minute ventilation response was not significantly ($p > 0.05$) different between R_0 and R_s experiments. Minute ventilation is commonly analyzed by its volume and timing components, tidal volume and breathing frequency (f). A more sophisticated analysis of the pattern of breathing is obtained by dividing minute ventilation into its mean inspiratory flow rate (\bar{V}_i , l min⁻¹) and duty cycle (T_i/T_{tot}). In figure 3 these components of minute ventilation are plotted as a function of $\dot{V}O_2$. The relationship between duty cycle and oxygen uptake was not significantly different from zero with the R_0 ($r = 0.26$) load. However, with the R_s load, respiratory duty cycle became highly ($p < 0.01$) correlated ($r = 0.67$) to oxygen uptake. Thus, progressively increasing exercise hyperpnea without added inspiratory load does not rely upon changes in the duty cycle to augment minute ventilation but addition of an inspiratory load elicits changes in the breath's timing components. The mean inspiratory flow was highly correlated ($r = 0.96$ and $r = 0.95$ for R_0 and R_s , respectively) to oxygen uptake. At low to moderate levels of $\dot{V}O_2$ (15-45 ml kg⁻¹ min⁻¹), the mean inspiratory flow was not affected by the addition of the R_s load. However, the R_s resistance did significantly ($p < 0.05$) depress the mean inspiratory flow at peak levels of exercise. Thus the mean inspiratory flow demonstrated greater sensitivity to the imposition of added inspiratory resistance than the duty cycle. Since the mean inspiratory flow rate is an index of the respiratory drive (10), these results suggest that this level of added inspiratory resistance was sufficient to reduce the force

generation of the respiratory muscles. Whether this was the result of a reflex inhibition of inspiratory drive at the respiratory center, spinal level or fatigue of the skeletal muscles is not known.

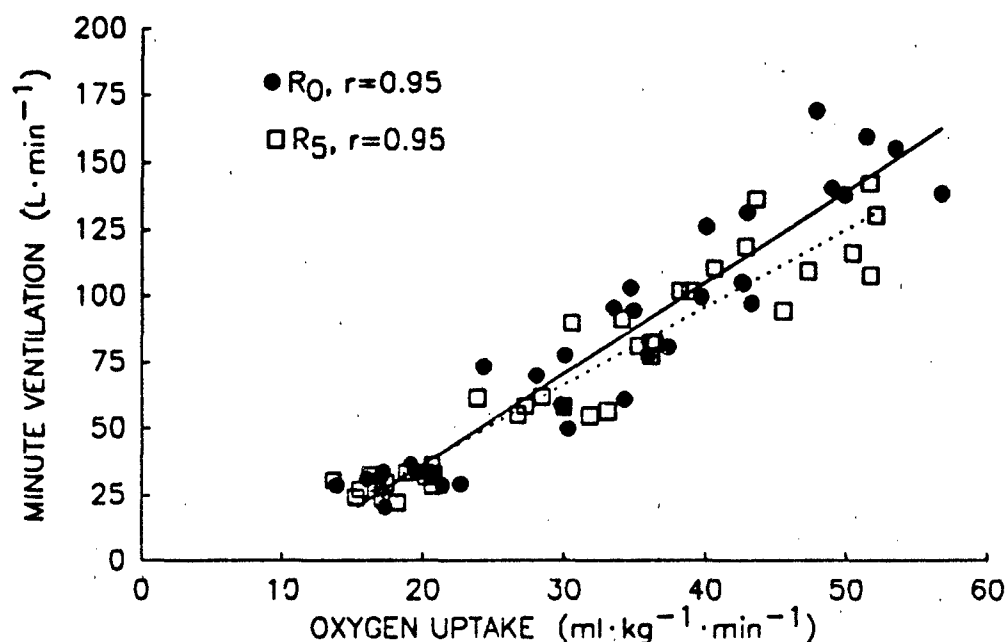


Fig. 2: Minute ventilation during progressive intensity exercise to fatigue as a function of oxygen uptake. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

The magnitude and pattern of the peak ventilatory response during maximum intensity exercise was related to each subject's hypercapnic responsiveness. As shown in figure 4, peak minute ventilation was highly correlated ($r=0.82$, $p<0.01$) to hypercapnic responsiveness (slope=15.9) and the imposition of the R_5 resistance significantly ($p<0.05$) reduced this relationship (slope=10.9, $r=0.83$). The peak mouth pressure (Fig. 5) was also significantly ($p<0.01$) correlated to hypercapnic responsiveness with both R_0 ($r=0.73$) and R_5 ($r=0.87$) loads. As expected, the peak mouth pressures were significantly higher against the R_5 load. Analysis of the breathing pattern yielded a significant ($p<0.01$) correlation between mean inspiratory flow and hypercapnic responsiveness with either R_0 ($r=0.78$) or R_5 ($r=0.76$) inspiratory resistance (Fig. 6), but no significant correlation ($r=0.15$ and $r=0.17$ for R_0 and R_5 respectively) with duty cycle.

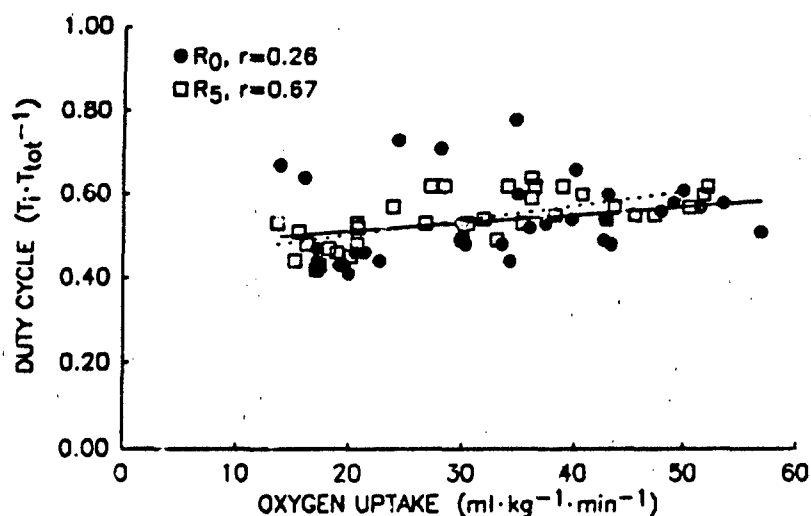


Fig. 3a: Respiratory duty cycle during progressive intensity exercise to fatigue as a function of oxygen uptake. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

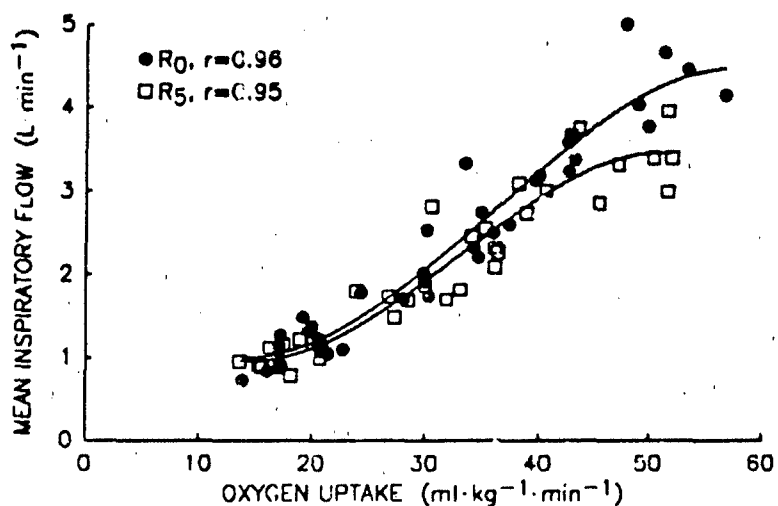


Fig. 3b: Respiratory mean inspiratory flow during progressive intensity exercise to fatigue as a function of oxygen uptake. Third order regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

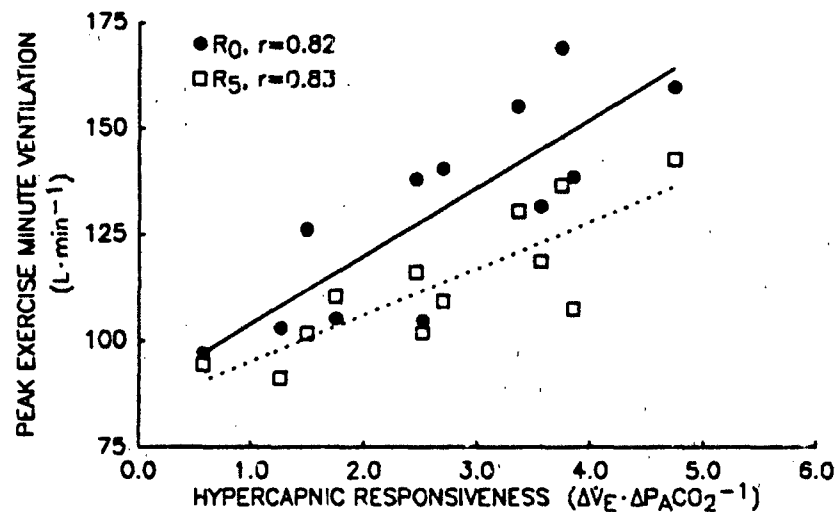


Fig. 4: Peak exercise minute ventilation during progressive intensity exercise to fatigue as a function of subjects' hypercapnic responsiveness. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

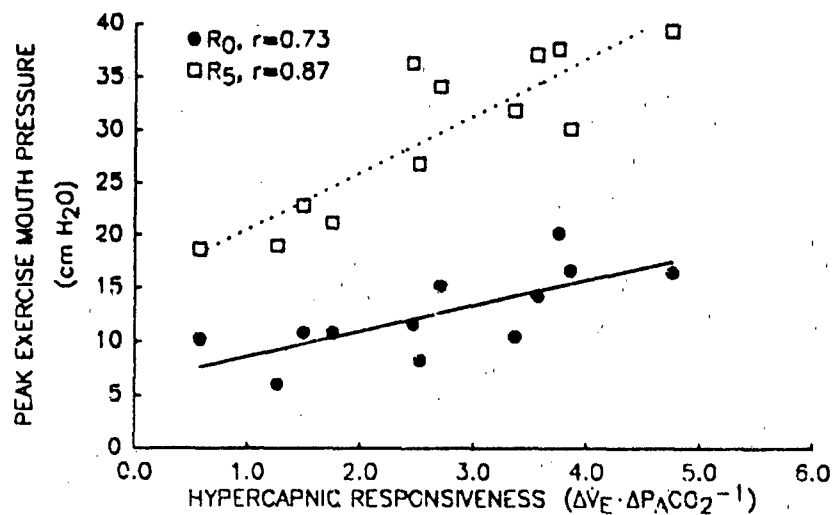


Fig. 5: Peak exercise mouth pressure during progressive intensity exercise to fatigue as a function of subjects' hypercapnic responsiveness. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

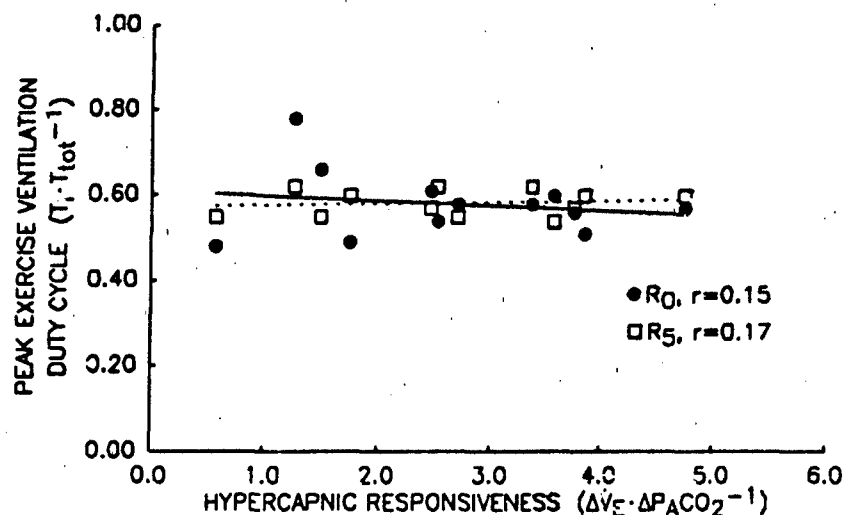


Fig. 6a: Peak exercise respiratory duty cycle during progressive intensity exercise to fatigue as a function of subjects' hypercapnic responsiveness. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

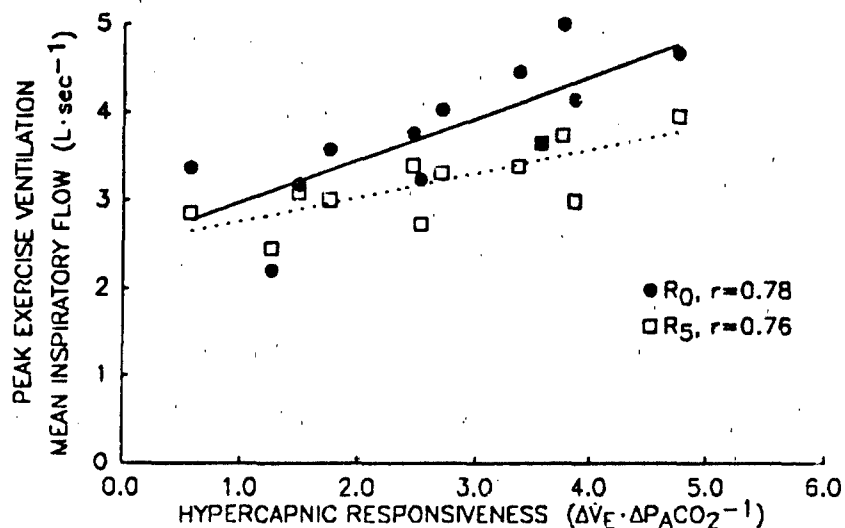


Fig. 6b: Peak exercise mean inspiratory flow during progressive intensity exercise to fatigue as a function of subjects' hypercapnic responsiveness. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

The data in figures 4-6 suggest that a major determinate of the magnitude of the exercise ventilatory response is each individual's central chemoreceptor's and respiratory control center's sensitivity to CO_2 . This finding is consistent with a previous report (29). Additionally, our data demonstrates that imposition of a mild inspiratory resistance does alter this relationship. It is interesting that the breathing cycle timing was not correlated to hypercapnic responsiveness and only correlated to oxygen uptake when inspiratory resistance was added. Proprioceptors in the respiratory muscles have been shown to modulate force development via spinal and supraspinal reflexes, but not respiratory cycle timing (39). Given the peak mouth pressures generated against the R_i load (Fig. 5), the respiratory muscles were generating over twice the force to produce the peak exercise minute ventilation with the R_i compared to the R_o load. These forces were certainly being transduced by respiratory muscle tendon organs. Therefore, the lack of any alteration of duty cycle with this level of added inspiratory resistance is consistent with the model of muscle proprioceptors modulating force development alone (i.e. mean inspiratory flow) and not breathing cycle timing.

VENTILATORY AND METABOLIC RESPONSES TO STEADY-STATE SUBMAXIMAL EXERCISE

The group mean (\pm S.D.) ventilatory responses to sustained (30 min), submaximal (60% peak $\dot{V}\text{O}_2$), steady-state exercise with R_o and R_i are presented in figures 7-9. With the R_o load, over the 30 minute exercise period minute ventilation gradually increased ($p<0.01$), while tidal volume (Fig 8), and inspiratory and expiratory times decreased ($p<0.01$). The minute ventilation increase was due to an increased mean inspiratory flow ($p<0.01$) since the duty cycle was unchanged (Fig. 9). Since the end tidal PCO_2 decreased ($p<0.01$) during the exercise period, the increased mean inspiratory flow and minute ventilation may have been stimulated by a decreased arterial pH due to lactate flux from the exercising skeletal muscles.

Added inspiratory resistance (R_i) did not significantly alter the exercise minute ventilation but did alter the pattern of breathing throughout the 30 minute exercise period. Breathing against the added inspiratory resistance increased ($p<0.01$) the duty cycle (Fig. 9) by prolonging inspiratory duration ($p<0.01$). However, mean

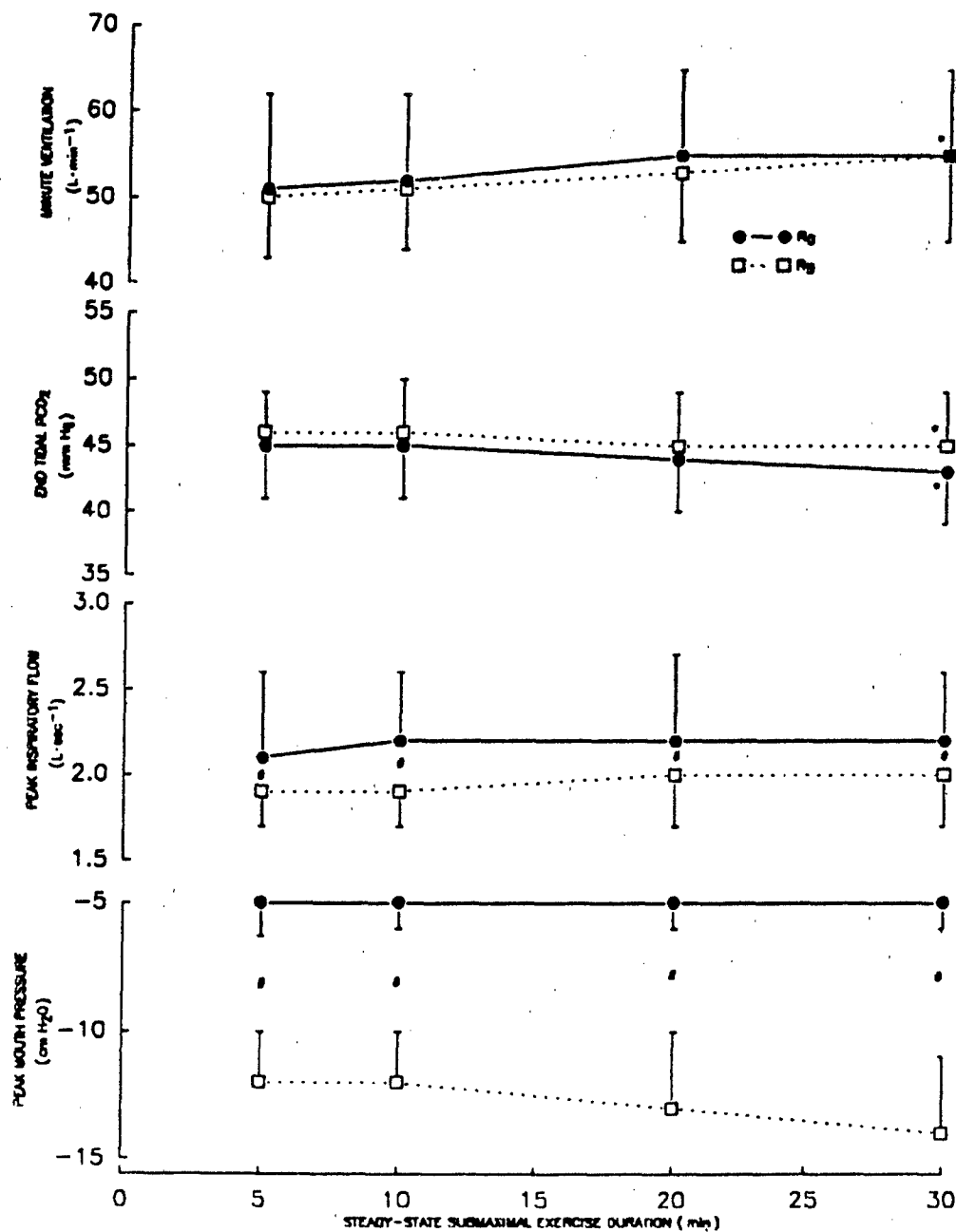


Fig. 7: Ventilatory parameters (mean \pm S.D.) during submaximal steady-state exercise as function of exercise duration. Differences ($p < 0.05$) from 5 min values across time are indicated by (*) and differences between R_0 and R_5 by (#).

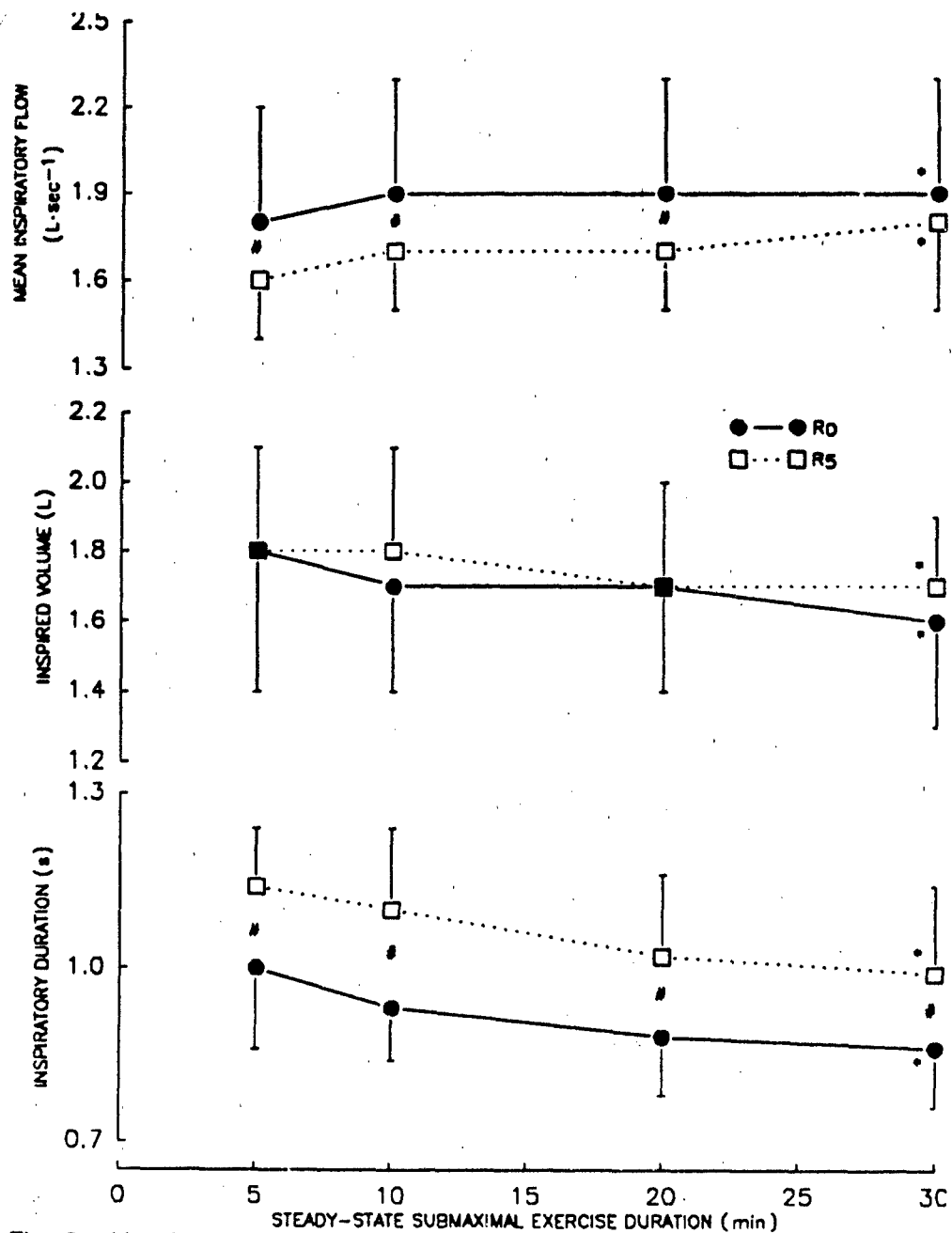


Fig. 8: Ventilatory parameters (mean \pm S.D.) during submaximal steady-state exercise as function of exercise duration. Differences ($p < 0.05$) from 5 minute values across time are indicated by (*), differences between R_0 and R_5 by (#).

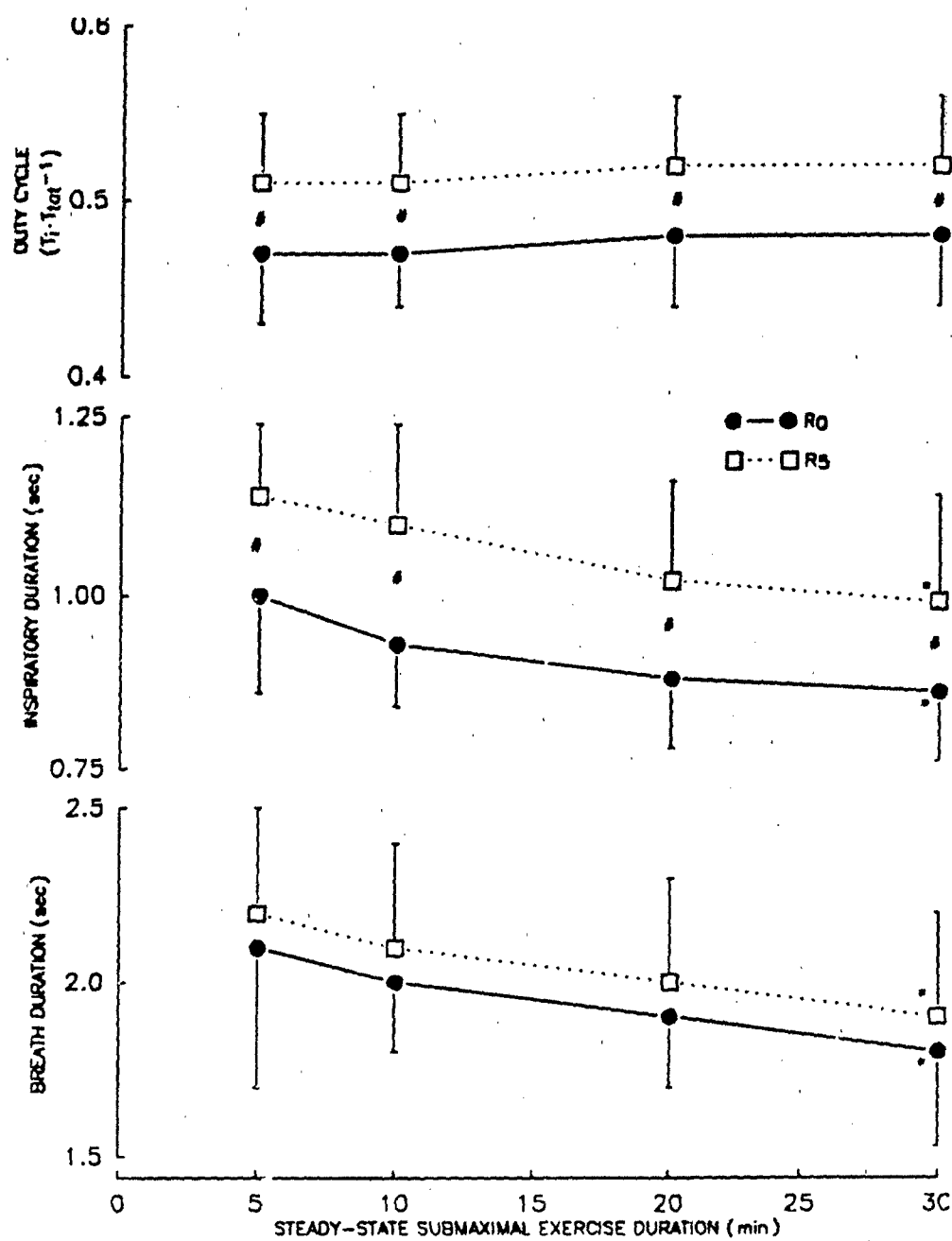


Fig. 9: Ventilatory parameters (mean \pm S.D.) during submaximal steady-state exercise as function of exercise duration. Differences ($p < 0.05$) from 5 minute values across time are indicated by (*), differences between R_0 and R_5 by (#).

inspiratory flow was lower ($p < 0.05$) due to the longer inspiratory duration but unchanged inspired volume when breathing against the R_i load (Fig. 8). These counteracting changes in duty cycle and mean inspiratory flow resulted in similar ($p > 0.05$) exercise minute ventilations for both inspiratory load (R_o and R_i) conditions. The peak mouth pressure generated to overcome the inspiratory resistance was, as expected, greatly elevated ($p < 0.01$) by the R_i load (Fig. 7). Over the duration of the steady-state exercise with the R_i load, the changes in ventilatory responses (Fig. 7-9) were similar to those observed with the R_o load. Generally, minute ventilation increased ($p < 0.05$) via increased mean inspiratory flow ($p < 0.01$) probably due to a rise of lactate in the arterial blood.

These results suggest that imposition of this level of inspiratory resistance does not alter the relationship between steady-state metabolic demand and the respiratory pump. However, the respiratory controller responds to the added inspiratory load by altering the pattern of breathing to minimize this perturbation to the work of breathing, while maintaining a level of ventilation sufficient to meet the metabolic demand. The imposition of the R_i load increased the resistive work component of breathing. Consequently, the pattern of breathing was modified to minimize the increase in the work of breathing by reducing the inspiratory flow rate but prolonging inspiratory duration to maintain adequate alveolar ventilation.

To further analyze the ventilatory response to steady-state exercise, the ventilatory parameters measured at minutes 10, 15 and 20 were averaged together and are presented in Figures 10-14. The minute ventilations achieved during the middle third of the steady-state exercise with the R_o load were related ($r = 0.81$, $p < 0.01$) to the subjects' hypercapnic responsiveness (Fig. 10). Nonetheless, no significant correlations ($p > 0.05$) were observed (fig. 11-12) between the subjects' resting CO_2 sensitivity and: peak mouth pressure ($r = 0.41$), mean inspiratory flow ($r = 0.46$); or duty cycle ($r = 0.32$). However, when breathing against the R_i load, exercise ventilatory responses became more closely related to each subject's hypercapnic responsiveness. Exercise minute ventilation was significantly ($p < 0.01$) correlated ($r = 0.89$) to subjects' CO_2 sensitivity (fig. 10). Likewise, the peak mouth pressures generated against the added inspiratory resistance demonstrated a significant ($p < 0.01$) relationship ($r = 0.71$). When the R_i load was present, mean inspiratory flow became significantly correlated ($r = 0.75$, $p < 0.01$) to hypercapnic responsiveness, but the ventilatory duty cycle ($r = 0.28$, $p > 0.05$) did not.

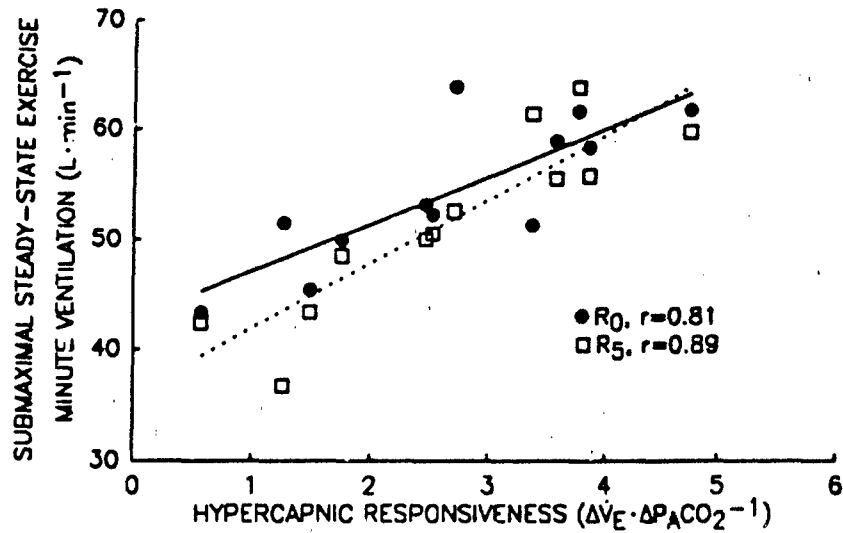


Fig. 10: Minute ventilation during middle third of the submaximal steady-state exercise as a function of subjects' hypercapnic responsiveness. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

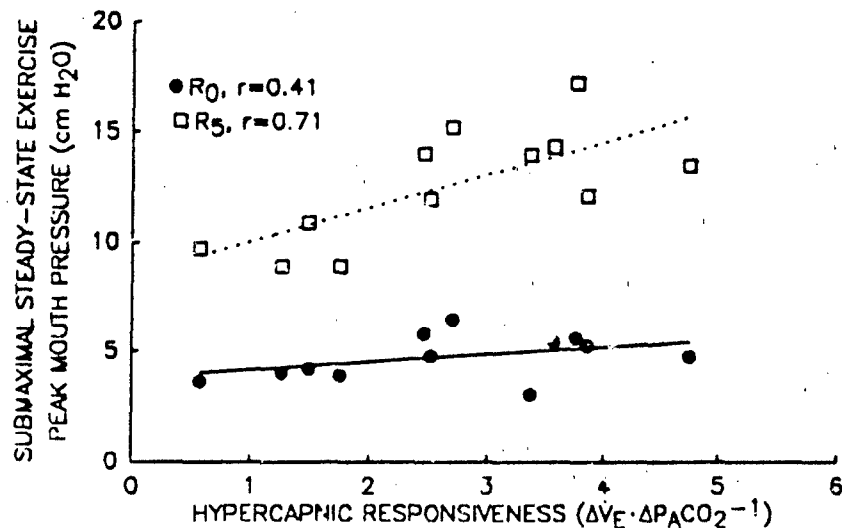


Fig. 11: Peak mouth pressure during middle third of the submaximal steady-state exercise as a function of subjects' hypercapnic responsiveness. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

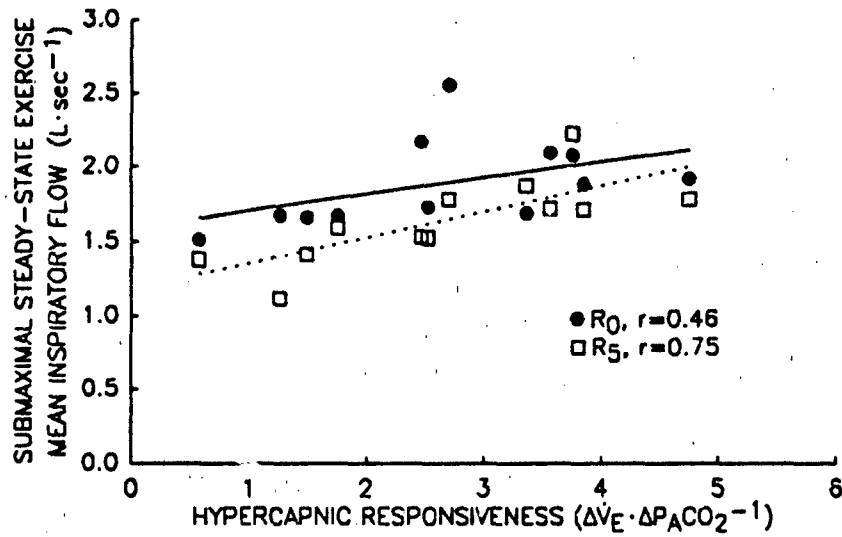


Fig. 12a: Mean inspiratory flow during middle third of the submaximal steady-state exercise as a function of subjects' hypercapnic responsiveness. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

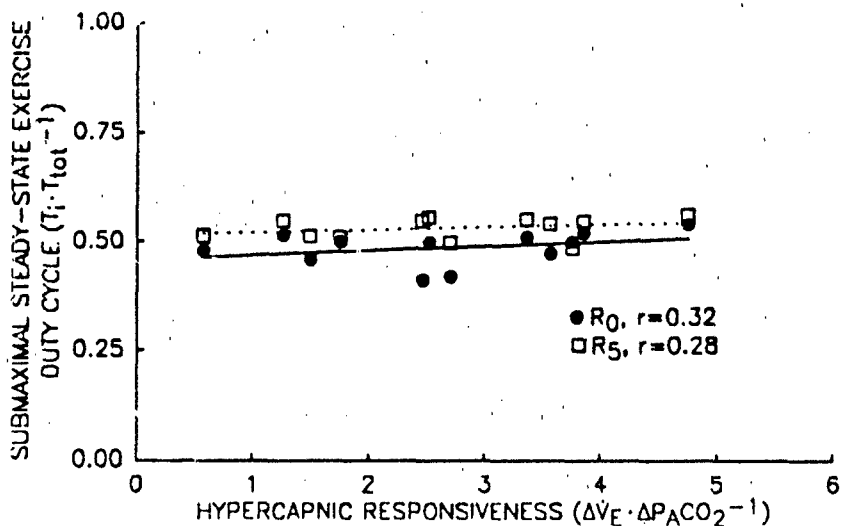


Fig. 12b: Respiratory duty cycle during middle third of the submaximal steady-state exercise as a function of subjects' hypercapnic responsiveness. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

Since, mean inspiratory flow is an index of ventilatory drive (10), during submaximal exercise with added inspiratory resistance the primary factor setting the ventilatory drive-metabolic demand relationship is the ventilatory controller's sensitivity to CO_2 .

A specific aim of the steady-state exercise protocol was to test the hypothesis that subjects with high perceptual sensitivity to added inspiratory resistance would alter their pattern of breathing in order to minimize adverse respiratory sensations (ie. dyspnea, difficulty breathing, etc.). As previously shown (Figures 7-9), imposition of the R_i load caused the subjects to modify the respiratory volume and timing components used to achieve exercise hyperpnea. However, it appears that each subject's perceptual sensitivity to added air flow resistance did not significantly contribute to shape their pattern of breathing in response to added inspiratory resistance during exercise. As seen in figure 13, exercise ventilation with minimal inspiratory resistance (R_{i0}) was not significantly ($p > 0.05$) related to subjects' magnitude estimation of added air flow resistance ($r = 0.54$). When breathing against elevated inspiratory resistance (R_i), weak but significant ($p < 0.05$) correlations appeared between magnitude estimation of air flow resistance and exercise: minute ventilation ($r = 0.64$); peak mouth pressure ($r = 0.59$); and mean inspiratory flow ($r = 0.68$) (Figures 12-13). However, since magnitude estimation of added resistance was also significantly correlated to hypercapnic responsiveness, it is likely that the relationships observed between magnitude estimation and exercise ventilation were secondary to the relationship with hypercapnic responsiveness. This conclusion is further strengthened by the fact that when steady-state exercise minute ventilation or the mean inspiratory flow are modeled as a function of the subjects' hypercapnic responsiveness and magnitude estimation of added resistance in a stepwise, multiple regression procedure, the correlations are not improved by the addition of the magnitude estimation variable ($p > 0.05$). Finally, the lack of a relationship may be explained if the psychophysical tests used were not sufficiently discriminative or sensitive enough to assess the subjects' perceptual sensitivity to respiratory mechanical loads.

Immediately before and after the steady-state exercise, each subject answered an environmental symptoms questionnaire. Generally, as expected, subjects reported increased symptoms associated with fatigue following exercise. Following steady-state submaximal exercise with R_{i0} , no respiratory related symptom was scored significantly ($p < 0.05$) higher than the pre-exercise baseline.

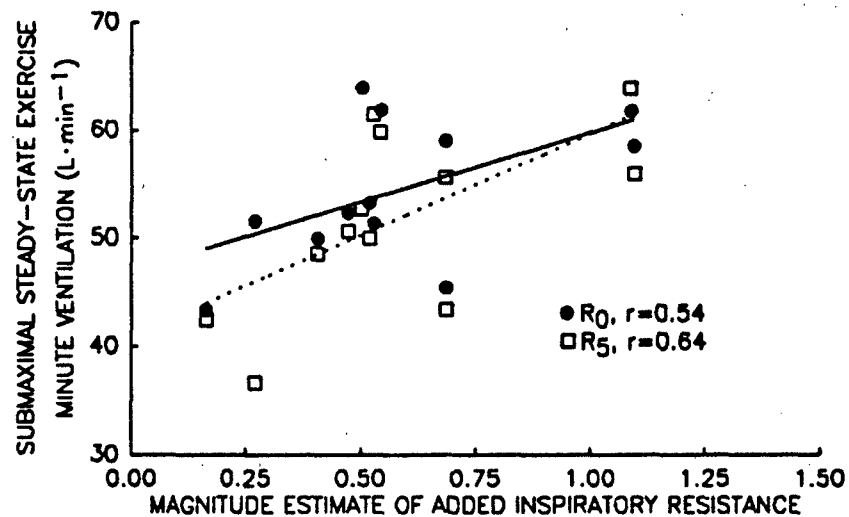


Fig. 13a: Minute ventilation during middle third of the submaximal steady-state exercise as a function of subjects' ME. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

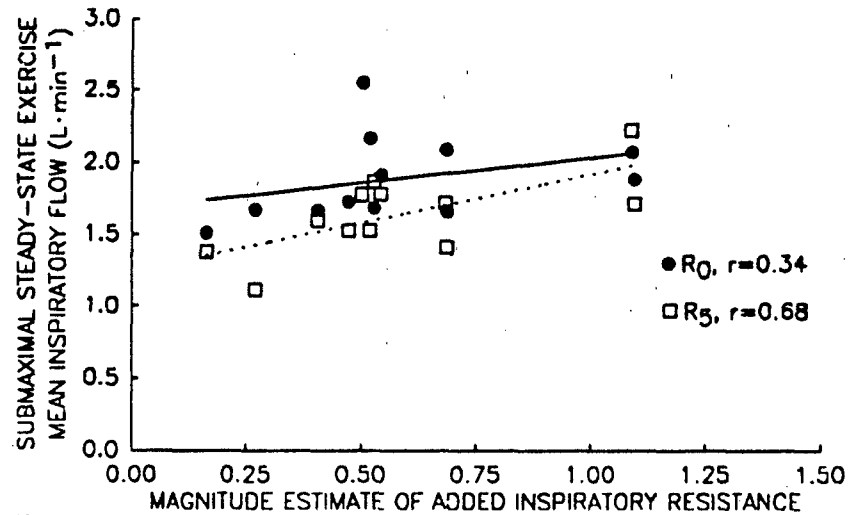


Fig. 13b: Mean inspiratory flow during middle third of the submaximal steady-state exercise as a function of subjects' ME. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

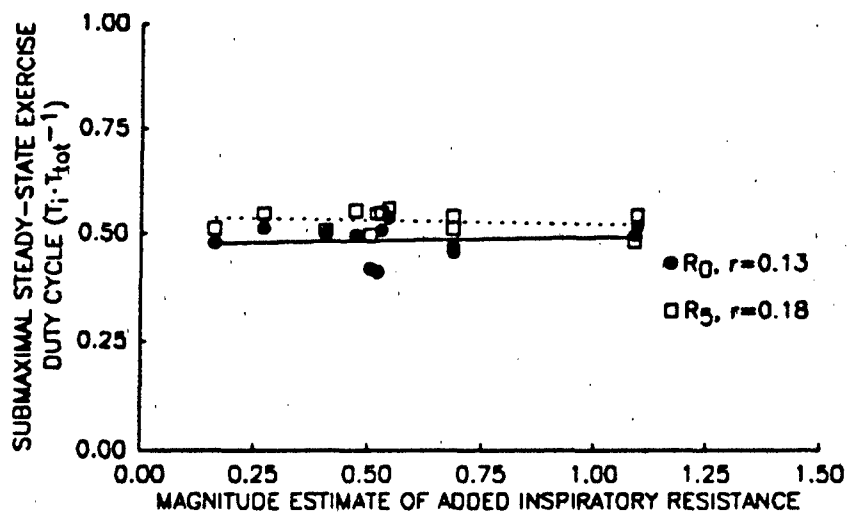


Fig. 13c: Respiratory duty cycle during middle third of the submaximal steady-state exercise as a function of subjects' ME. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

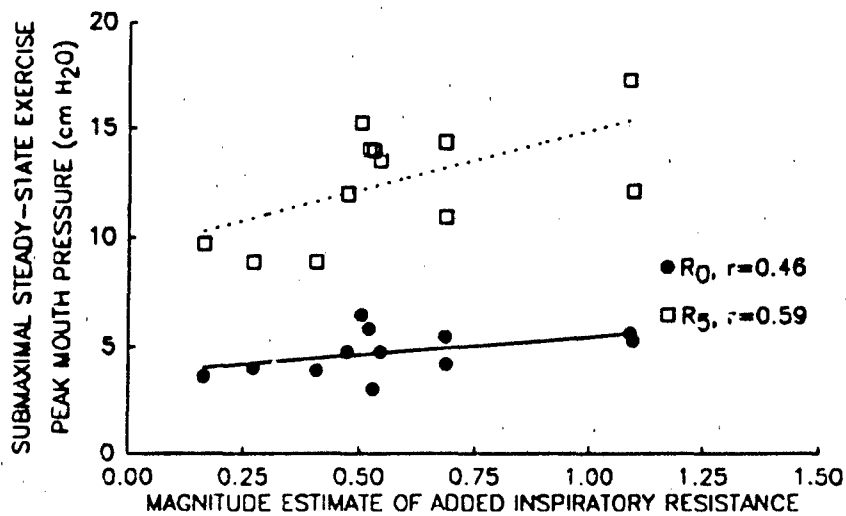


Fig. 13d: Peak mouth pressure during middle third of the submaximal steady-state exercise as a function of subjects' ME. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

However, following exercise with the R_5 inspiratory load condition, the symptom "Hard to Breathe" was scored significantly ($p < 0.05$) higher than its pre-exercise baseline level and the companion score obtained following exercise with R_0 . On the other hand, the symptom "Difficulty Breathing" was not significantly altered by breathing against the R_5 load. Of interesting note is the finding that the subjects' perception of "Hard to Breathe" during exercise with R_5 was significantly ($p < 0.05$) correlated ($r = 0.66$) with the subjects' perceptual sensitivity to added inspiratory resistance (Fig. 14). This result suggests that perceptual sensitivity to inspiratory resistance does influence an individual's perception of breathing during exercise and possibly their behavioral control of ventilation and ultimately work performance. Although our study did not find that the subjects' perception of effort to breath during steady-state submaximal exercise significantly modified exercise tolerance, possibly with longer duration and/or different types of exercise, perception of breathing effort may modify exercise intensity or tolerance.

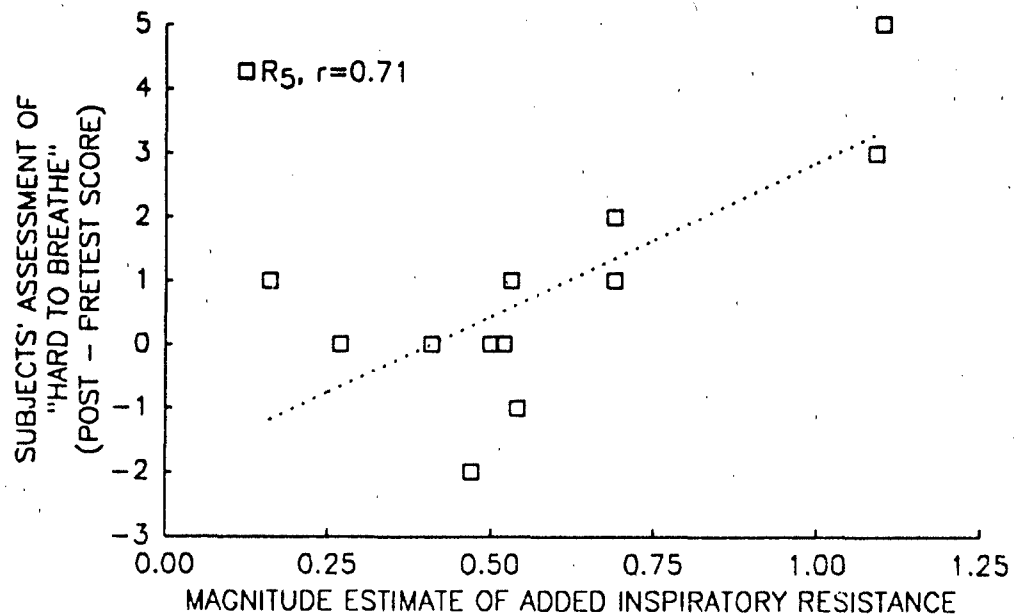


Fig. 14: Subjects' perception of "Hard to Breathe" during submaximal steady-state exercise with R_5 , plotted as a function of their ME. The subjects' score was computed by subtracting their pre-exercise score from their post-exercise score.

WORK LOAD RESPONSES TO CONSTANT EFFORT EXERCISE

The specific aim of these experiments were to test the hypothesis that added resistance to breathing decreases the power output performed by increasing the perception of effort. By using the power output performed as a measure of the subject's perception of effort, over the 30 minute exercise period both the magnitude and temporal pattern of the subjects' perception of effort were quantified. Generally, as exercise duration increased, power output decreased ($p < 0.05$, Fig. 15). This response was observed for both inspiratory load conditions (R_0 and R_5). However, no significant differences ($p > 0.05$) were observed between the constant effort power output curves when breathing against the two inspiratory resistances. That our subjects decreased their power output with increasing exercise duration is consistent with the study by Pandolf and Cain (33). However, we had hypothesized that the imposition of the R_5 load would increase the subjects' sense of effort resulting in a greater reduction in power output over time compared to the R_0 condition.

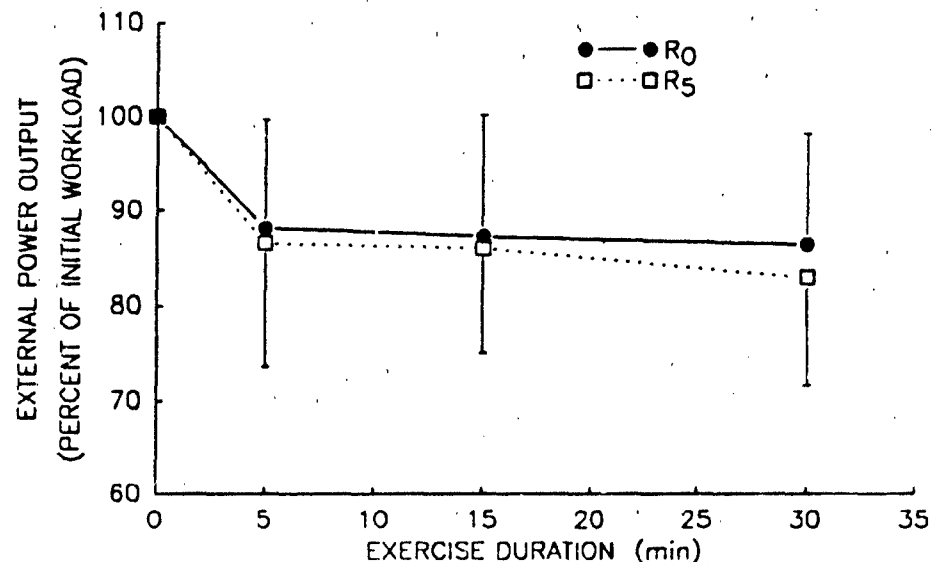


Fig. 15: External power output during constant effort exercise plotted as a function of exercise duration. Power output is normalized to the initial power output.

As previously stated and illustrated in figure 14, the addition of the R_s load during steady-state submaximal exercise increased the subjects perception of "hard to breathe". The subjects' initial power output during constant effort exercise was identical to the power output they maintained during the steady-state submaximal exercise protocol. Therefore, it is reasonable to assume that during the constant effort exercise protocol the subjects had similar "hard to breathe" sensations. Yet these sensations did not influence their perception of the effort to maintain exercise.

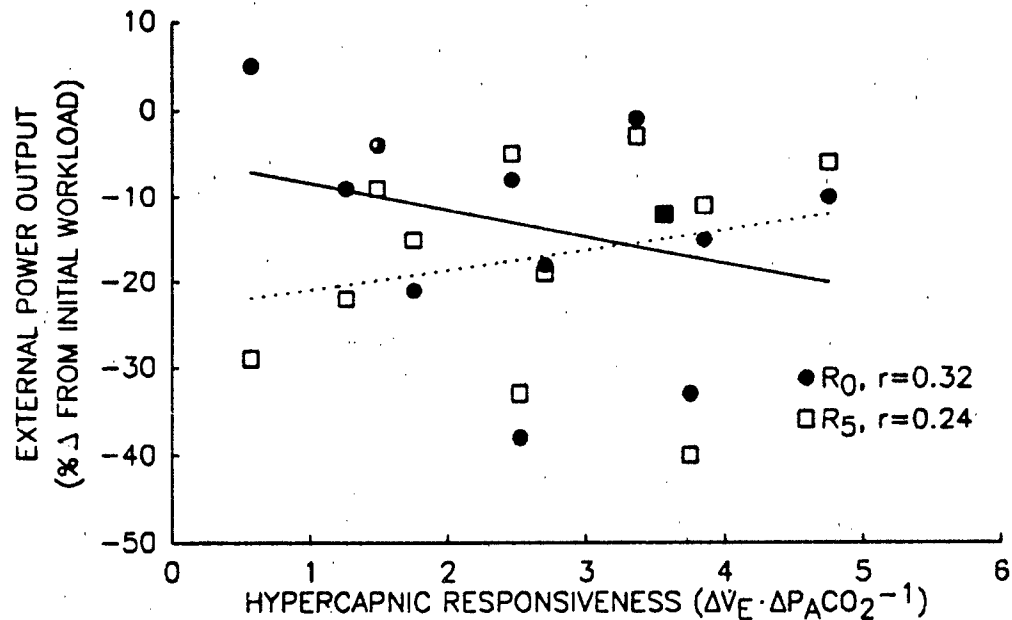


Fig. 16: Percent change of power output from beginning to end of constant effort exercise as a function of subjects' hypercapnic responsiveness. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

We hypothesized that subjects with high sensitivity to CO_2 and or added inspiratory resistance would produce greater decrements in their constant effort power output curves. However, our results did not support this hypothesis. In figures 17 and 18, the constant effort power output change between exercise minutes 1 and 28 are plotted as a function of hypercapnic responsiveness and perceptual sensitivity to added inspiratory resistance respectively. No significant ($p>0.05$) correlations were observed between constant effort power output and either hypercapnic responsiveness ($r=0.32$ and $r=0.24$ for R_0 and R_5 respectively) or

magnitude estimation of added resistance ($r=0.39$ and $r=0.02$ for R_0 and R_5 respectively). Therefore, over the duration of this exercise, ventilatory sensitivity to hypercapnia or added resistance did not appear to influence the level of perceived effort during exercise.

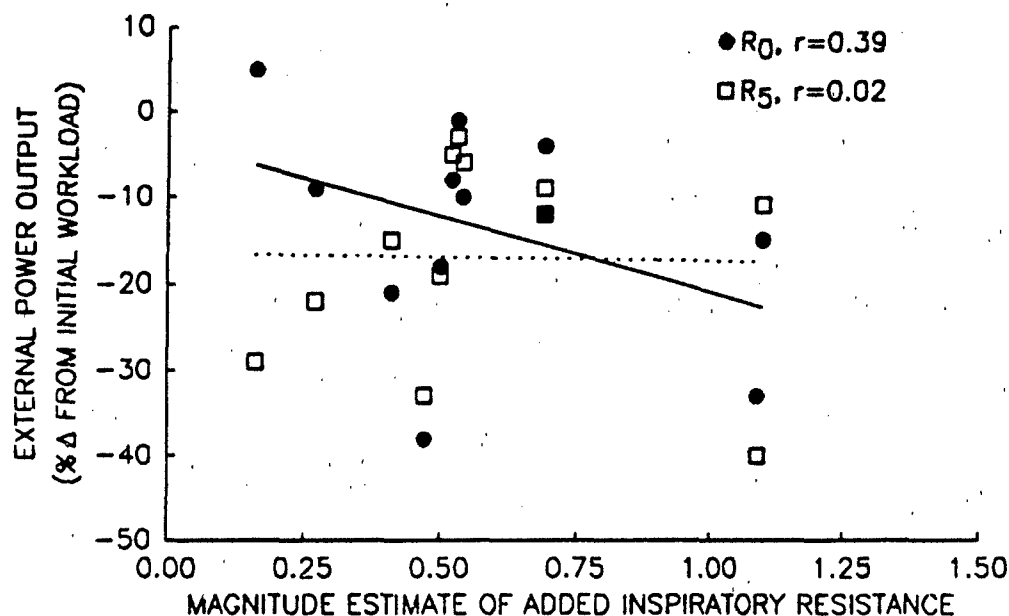


Fig. 17: Percent change of power output from beginning to end of constant effort exercise as a function of subjects' ME. Linear regression analysis plotted for load R_0 (solid line) and R_5 (dotted line).

CONCLUSIONS

This study examined the effect of added inspiratory resistance on breathing patterns and work performance during: progressive intensity exercise; steady-state exercise and constant effort work. Its aim was to determine the relationship between respiratory sensations and hypercapnic responsiveness to exercise breathing patterns and work performance. We found that mild inspiratory resistance ($5 \text{ cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{sec}^{-1}$) did not alter peak oxygen uptake, peak external work performed, or steady-state submaximal work duration. However, during progressive intensity

exercise, changes in the pattern of breathing, particularly a reduction of mean inspiratory flow (an index of respiratory drive) occurred with the imposition of the inspiratory resistance, whereas, the breathing cycle timing components were relatively unchanged. During submaximal steady-state exercise, added inspiratory resistance decreased mean inspiratory flow but prolonged the duty cycle thus maintaining minute ventilation. Despite its effects on breathing pattern and respiratory work, imposition of added inspiratory resistance did not affect constant effort functions to cycle ergometry, suggesting that perception of respiratory effort did not significantly influence the perceived effort of the exercise task.

Exercise minute ventilation was found to be strongly correlated to subjects' ventilatory hypercapnic responsiveness. This is consistent with previous reports. We demonstrated that of the components of minute ventilation, timing and respiratory drive, the latter was correlated to hypercapnic responsiveness but the former was not during both maximal intensity and submaximal exercise tasks. The subjects' perception of added inspiratory resistance did affect their pattern of breathing when added inspiratory loads were present. However, the ventilatory responsiveness to hypercapnia was the stronger determinant of exercise ventilation and the associated pattern of breathing. Although not a strong determinant of their exercise breathing pattern, each subject's magnitude estimate of added inspiratory resistance did apparently influence their sense of how hard it was to breathe during submaximal exercise. It has been suggested (1) that perception of difficulty breathing or dyspnea is more closely related to the sense of effort rather than the actual muscle force produced. If this is true, then increasing one's respiratory muscle strength may reduce the sense of effort to breathe while wearing a CB mask. However, this relationship has not been studied.

RECOMMENDATIONS

The U.S. Army must be prepared to engage in military operations in a nuclear, biological and chemical contaminated environment. During these operations soldiers wearing MOPP gear will engage in a variety of tasks that require physical exercise.

It is well established that exercise performance is reduced while wearing the CB mask. As a result, the U.S. Army is interested in methods to improve exercise performance when breathing is opposed. The finding that both submaximal and maximal exercise minute ventilation is strongly correlated to subjects' ventilatory hypercapnic responsiveness, suggests it may be possible to screen soldiers who maybe more prone to work performance decrements when wearing a CB mask. Moreover, the observation that one of the components of minute ventilation, respiratory drive, was correlated both to oxygen uptake and hypercapnic responsiveness during submaximal and maximal exercise, suggests that respiratory muscle strength training programs may help to alleviate the adverse respiratory sensations experienced by soldiers wearing CB masks by increasing the subject's maximal respiratory drive. However, whether increasing respiratory muscle strength will alleviate a person's perception of "Hard To Breathe" is unknown. Further research into screening programs and if respiratory muscle training improves the pattern of exercise hyperpnea with concomitant amelioration of adverse respiratory sensations will need to be done.

REFERENCES

1. Altose, M., A. Dimarco, S. Gottfried and K. Strohl. The sensation of respiratory muscle force. Am.Rev.Respir.Dis. 126:807-811,1982.
2. Axen, K., S.S. Haas, F. Haas, D. Gaudino and A. Haas. Ventilatory adjustments during sustained mechanical loading in conscious humans. J.Appl.Physiol. 55:1211-1218,1983.
3. Bai, T.R., B.J. Rabinovitch and R.L. Pardy. Near-maximal voluntary hyperpnea and ventilatory muscle function. J.Appl.Physiol. 57(6):1742-1748,1984.
4. Bellemare, F. and A. Grassino. Effect of pressure and timing of contraction on human diaphragm fatigue. J.Appl.Physiol. 53(5):1190-1195,1982.
5. Bellemare, F. and A. Grassino. Evaluation of human diaphragm fatigue. J.Appl.Physiol. 53(5):1196-1206,1982.
6. Bentley, R.A., O.G. Griffen, R.G. Love, D.C.F. Muir and K.F. Sweetland. Acceptable levels for breathing resistance of respiratory apparatus. Arch.Environ.Health 27:273-280,1973.
7. Burki, N.K., K. Mitchell, B.A. Chaudhary and F.W. Zechman. The ability of asthmatics to detect added resistive loads. Am.Rev.Respir.Dis. 117:71-75,1978.
8. Burki, N.K., P.W. Davenport, F. Safdar and F.W. Zechman. The effects of airway anesthesia on magnitude estimation of added inspiratory resistive and elastic loads. Am.Rev.Respir.Dis. 127:2-4,1983.
9. Burki, N.K. Effects of bronchodilation on magnitude estimation of added resistive loads in asthmatic subjects. Am.Rev.Respir.Dis. 129:225-229, 1984.
10. Bye, P.T.P., G.A. Farkas and C.H. Roussos. Respiratory factors limiting exercise. Ann.Rev.Physiol. 45:439-51,1983.
11. Campbell, E.J.M., S.C. Gandivia, K.J. Killian, C.K. Mahutte and J.R.A. Rigg. Changes in the perception of inspiratory resistive loads during partial curarization. J.Physiol.(London) 309:93-100,1980.
12. Cerretelli, P., S. Rajinder and L. Farhi. Effect of increased airway resistance on ventilation and gas exchange during exercise. J.Appl.Physiol. 27:597-600,1969.
13. Cooper, E.A. Suggested methods of testing and standards of resistance for respiratory protective devices. J.Appl.Physiol. 15:1053-1061,1960.
14. Craig, F.N., W.V. Blevin and H.L. Froehlich. Training to improve endurance in exhausting work of men wearing protective masks: A review of some preliminary experiments (TR #N72-14127), AFSC, WPAFB, OH.1971.

15. Cummings, E.G., W.V. Blevins, C.M. Greenland and F.N. Craig. Effects of protective masks on soldier's ability to run a half mile. CWLR 2254, Edgewood Arsenal, 1958.
16. Daubenspeck, A. and F.M. Bennett. Immediate human breathing pattern responses to load near the perceptual threshold. J.Appl.Physiol. 55:1160-1166,1983.
17. Demedts M. and N.R. Anthonisen. Effects of increased external airway resistance during steady-state exercise. J.Appl.Physiol. 35:361-366,1973.
18. D'Urzo, A.D., K.R. Chapman and A.S. Rebuck. Effect of inspiratory resistive loading on control of ventilation during progressive exercise. J. Appl. Physiol. 62:134-140, 1987.
19. Gottfried, S.B., M.D. Altose, S.G. Kelsen and N.S. Cherniack. Perception of changes in airflow resistance in obstructive pulmonary disorders. Am.Rev.Respir.Dis. 124:566-570,1981.
20. Hermansen L., Z. Vokac and P. Lereim. Respiratory and circulatory response to added airflow resistance during exercise. Ergonomics 15:15-24,1972.
21. Hesser, C.M., D. Linnarsson and L. Fagraeus. Pulmonary mechanics and work of breathing at maximal ventilation and raised air pressure. J.Appl.Physiol. 50:747-753,1981.
22. Hondous, T.K., L. Petsork, C. Boyles, J. Hankinson and H. Amandus. Effects of added resistance to breathing during exercise in obstructive lung disease. Am.Rev.Respir.Dis. 128:943-948,1983.
23. Johnson, A.T. and E.G. Cummings. Mask design considerations. Am.Ind.Hyg.Assoc.J. 36:220-228,1975.
24. Johnson, A.T. and H.M. Berlin. Exhalation time characterizing exhaustion while wearing respiratory protective masks. Am.Ind.Hy.Assoc.J. 35:463,1974.
25. Killian, K.J., C.K. Mahutte and E.J.M. Campbell. Resistive load detection during passive ventilation. Clin.Sci. 59:493-495,1980.
26. Killian, K.J., C.K. Mahutte and E.J.M. Campbell. Magnitude scaling of externally added loads to breathing. Am.Rev.Respir.Dis. 123:12-15,1981.
27. Killian, K.J., D.D. Bucens and E.J.M. Campbell. Effect of breathing patterns on the perceived magnitude of added loads to breathing, J.Appl.Physiol. 52:578-584,1982.
28. Lotens, W.A. Physiological strain: Clothing, physical load and military performance. In: Aspectqs Medicaus et Biophysiques des Vetements Deprotection. pp 268-279,1983.

29. Martin, B.J., J.V. Weil, K.E. Sparks, R.E. McCullough and R.F. Grover. Exercise ventilation correlates positively with ventilatory chemoresponsiveness. J.Appl.Physiol. 45:557-564, 1978.
30. Muza, S.R., S. McDonald and F.W. Zechman. Relationship between perceptual performance and load compensation responses to added inspiratory resistance. Fred.Proc. 42:331,1983.
31. Muza, S.R. and F.W. Zechman. Scaling of added loads to breathing: magnitude estimation vs. handgrip matching. J.Appl.Physiol. 57:888-891,1984.
32. Muza, S.R. A review of biomedical aspects of CB masks and their relationship to military performance. Tech. Rpt #1-87, U.S. Army Research Institute of Environmental Medicine, Natick, MA 01750, 1987.
33. Pandolf, K.B. and W.S. Cain. Constant effort during static and dynamic muscular exercise. J. Motor Behav. 6:101-110, 1974.
34. Pardy, R.L. and P.T. Bye. Diaphragmatic fatigue in normoxia and hyperoxia. J.Appl.Physiol. 58:738-742,1985.
35. Raven, P.B., A.T. Dodson and T.O. Davis. The physiological consequences of wearing industrial respirators. A review. Am.Ind.Hyg.Assoc.J. 40:517-534,1979.
36. Read, D.J.C. A clinical method for assessing the ventilatory response to carbon dioxide. Aust.Ann.Med. 16:20-32,1967.
37. Roussos C. and P.T. Macklem. The respiratory muscles. New Eng.J.Med. 307:784-796,1982.
38. Scoggin, C.H., R.D. Doekel, M.H. Kryger, C.W. Zwillich and J.V. Weil. Familial aspects of decreased hypoxic drive in endurance athletes. J. Appl. Physiol. 44: 464-468, 1978.
39. Shannon R. and F.W. Zechman. The reflex and mechanical response of the inspiratory muscles to an increased airflow resistance. Respirat.Physiol. 16:51-69,1972.
40. Silverman, L.G., A.R. Yancey, L. Amory, L.J. Barney and R.C. Lee. Fundamental factors in the design of protective respiratory equipment: A study and an evaluation of inspiratory and expiratory resistances for protective respiratory equipment. (Report #5339). Office of Scientific Research and Development, United States War Research Agency, Washington, D.C.,1945.
41. Silverman, L., G. Lee, T. Plotkin, L.A. Sawyers and A.R. Yancey. Air flow measurements on human subjects with and without respiratory resistance at several work rates. Ind.Hyg.Occup.Med. 3:461-478,1951.

42. Smutok, M.A., M.S. Skrinar and K.B. Pandolf. Exercise intensity: regulation by perceived exertion. Arch.Phys.Med.Rehabil. 61:569-574,1980.
43. Tack, M., M.D. Altose and N.S. Cherniack. Effect of aging on the perception of resistive ventilatory loads. Am.Rev.Resp.Dis. 126:463-467,1982.
44. Wiley, R.L. and F.W. Zechman. Perception of added airflow resistance in humans. Respirat.Physiol. 2:73-87,1966/67.
45. Younes, M. and G. Kivinen. Respiratory mechanics and breathing during and following maximal exercise. J.Appl.Physiol. 57(6):1773-1782,1957.
46. Zechman, F.W. and R.L. Wiley. Afferent inputs to breathing: Respiratory sensations. Handbook of Physiology Section 3, The Respiratory System. Am.Physiol.Soc., In Press.

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